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The Brighton Collaboration: addressing the need for standardized case definitions of adverse events following immunization (AEFI)

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Abstract

To further scientific progress of immunization safety, comparability of data from clinical trials and surveillance systems is essential. Comparability requires the availability of standardized case definitions for adverse events following immunization (AEFI) and guidelines for case determination, recording and data presentation.

Method: International collaborative working groups, consisting of professional volunteers from developed and developing countries, conduct systematic literature reviews to develop 50–100 AEFI definitions. Case definitions are finalized after a comment period by a reference group consisting of organizations concerned with immunization safety, and will be disseminated via the world-wide-web and other means for free world-wide use.

Results: Literature reviews yielded substantial diversity in data collection and presentation. We have developed standardized case definitions together with guidelines for use in clinical trials and surveillance systems.

Conclusions: Diversity in safety methods leads to considerable loss of scientific information. We have built the necessary international network of currently about 300 participants from patient care, public health, scientific, pharmaceutical, regulatory and professional organizations to develop and assess standardized AEFI case definitions and guidelines. Evaluation studies, global implementation, ongoing definition development and a continuously growing network will be essential for the success of the collaboration.
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In keeping with the Hippocratic oath, "First Do No Harm", any medical intervention including vaccines should be shown safe and effective prior to widespread adoption. However, interventions are rarely 100% safe. The decision to immunize must therefore balance the risks versus the benefits within an appropriate context. For preventive public health interventions like immunizations this context includes factors such as the incidence and severity of the target disease, as well as real and perceived adverse events following immunization.

However, two critical factors require vaccines to be safer than most other medical interventions. First, vaccines typically are administered to healthy persons (commonly infants and young children). Thus, the tolerance for vaccine risks is lower than the tolerance for risks from drugs administered to ill and older persons. Second, immunizations frequently are recommended universally, and sometimes even mandated in large populations. In mature immunization programs, where sustained high coverage with an efficacious vaccine has led to near elimination of the target disease, safety concerns become even more prominent, since fewer and fewer persons have experienced the disease, but all persons are likely to have been immunized. Rigorous scientific data on vaccine safety are needed to optimize the benefit-risk ratio of vaccines and enable evidence-based decision-making

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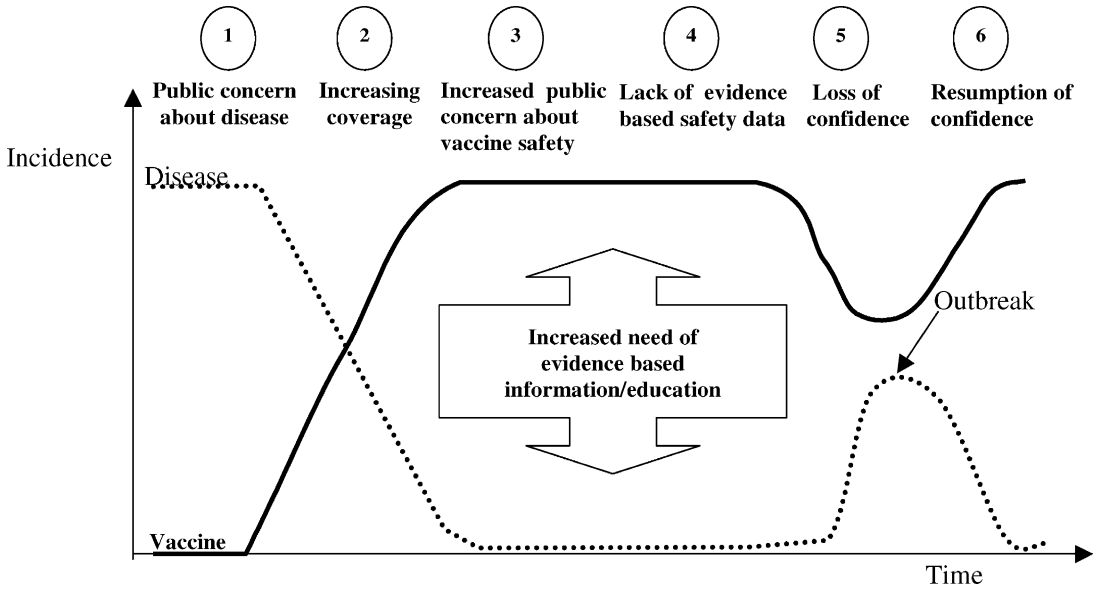

Fig. 1. The need for evidence-based information to balance the interaction of vaccine preventable disease, public concern and immunization rates (modified from Chen RT [32]).

on immunizations at both individual and societal level (Fig. 1).

Assessment of efficacy or effectiveness of vaccines is relatively straightforward, for example by comparing the incidence of the target disease among persons who received the immunization with those who did not. In contrast, vaccine safety cannot be measured directly; it can only be inferred indirectly by the absence or infrequency of measured adverse events. These events may differ by vaccine and may include currently unknown adverse events.

As some adverse events following immunization (AEFI) are rare, large sample sizes are needed for their detection and assessment. Most of the published vaccine trials have focused on assessment of efficacy and common adverse events. However, an appropriate sample size for this purpose is considerably smaller than that necessary to provide sufficient statistical power for the assessment of a vaccine's safety profile. In most of the pre-licensure trials, less than 5000–10,000 subjects receive a given vaccine. Given this sample size, the power of a study would be low to detect a significant difference between vaccinated and unvaccinated groups for events occurring at a rate of less than six per 10,000 vaccine recipients [1]. Events that would be important to detect may occur at lower frequencies (e.g. intussusception at 1/10,000 recipients). It is, therefore, essential for safety assessment to opt for larger sample sizes of trials and to maximize the ability to accumulate and compare safety data across trials. Data comparability for AEFI is optimized by the use of standardized case definitions, assessment techniques and observation times following immunization.

Table 1
Variability of case definitions for "fever" as AEFI exemplified in 10 prospective vaccine trials

Reference	Vaccine	Number of vaccine recipients	Temperature cut offs (°C)	Body site	Time of observation after immunization
King et al. 1996 [5]	MMR	386	>36.4 = hot to touch	Axillary	14 days
Shinefield et al.1998 [6]	MMR	609	≥38.8	Axillary/rectal/otic corrected for otic by axillary +1 °C and rectal −1 °C	42 days
Usonis et al. 1999 [7]	MMR	4712	≥38.1, >39.5	Rectal/axillary	42 days
Klinge et al. 2000 [8]	MMR	118	≥38.1, ≥39	N.S.	14 days
Crovari et al. 2000 [9]	MMR	1754	≥38.1, >39.5	Rectal	42 days
Gustafsson et al. 1996 [10]	DtaP vs. DTP vs. DT	9829	≥38, ≥40	Rectal	24 h + 14 days
Schmitt et al. 1996 [11]	DTaP vs. DTP vs. DT	22505	≥38, ≥39.5	Rectal	48 h + 8 days
Liese et al. 1997 [12]	DtaP vs. DTP vs. DT	16432	N.S.	N.S.	N.S.
Schmitt-Grohé et al. 1997 [13]	DTaP vs. DTP vs. DT	10271	≥38, ≥38.4, ≥40 [13]	Rectal	72 h
Simondon et al. 1997 [14]	DTaP vs. DTP	4181	>40.5 (as contraindication)	Rectal	Between 1 and 14 day

N.S.: not specified.

Table 2
Variability of case definitions for hypotonic hyporesponsive episodes (HHE) as AEFI exemplified in 10 vaccine studies

Reference	Vaccine	Sample size	Case definition/description	Time of observation after immunization
Ramkissoon et al. 1991 [15]	DTP	115	Term HHE used	14 days
Blumberg et al. 1993 [16]	DTP	60	Collapse episodes	48 h
Greco et al. 1996 [18]	DTaP (2x) vs. DTP vs. DT	15601	Term HHE used	48 h
Gustafsson et al. 1996 [10]	DTaP (2x) vs. DTP vs. DT	9829	Collapse characterized by limpness and pallor	48 h
Gold et al. 1997 [19]	DPT − Hib + OPV DPT + OPV DPT − IPV − Hib DPT − IPV	10	Sudden onset of two or more of the following: pallor, cyanosis, hyporesponsiveness or decreased muscle tone	48 h
Ueberall et al. 1997 [20]	DTaP vs. DTP vs. DT	10271	Collapse or shock like status (hypotonic hyporesponsive episode)	72 h
Olin et al. 1997 [21]	DTPa (3x) vs. DTPw	81835	Characteristically the child was pale, hypotonic and unresponsive to his parents [17]	48 h
Mills et al. 1998 [22]	DTP DPT-IPV + PRP-T DTP-IPV-PRP-T	560	Term HHE used	72 h
Goodwin et al. 1999 [23]	DTaP, DTP or DT	64	An episode of acute diminution of sensory awareness or loss of consciousness accompanied by pallor cyanosis and muscle hypotonicity	24–72 h
Gold et al. 2000 [24]	DPT, DTaP or aP ±Hib + OPV + HBV + MMR or DT or MMR	421	Sudden event characterized by hypotonia, hyporesponsiveness and pallor in the absence of a known cause such as a convulsion	48 h

Apart from a limited set of case definitions recommended by WHO in 1991, and dictionaries of terms used for pharmacovigilance (such as WHOART and MedDRA), there is a paucity of standardized, widely disseminated and globally accepted and implemented case definitions for AEFI [2,3]. A report of a US public health service workshop on hypotonic hyporesponsive episodes (HHE) after pertussis immunization is so far the only published structured work on an AEFI case definition [4]. Despite these limited attempts towards standardization of AEFI case definitions, most studies rely on ad hoc definitions, decreasing the ability to conduct combined or comparative analyses.

This diversity of case definitions and the variability of assessment methods and cut off points are illustrated for example with the AEFI “fever”. We reviewed published results from 10 large prospective vaccine trials of both killed and live attenuated vaccines (Table 1) [5–14]. In these trials of Measles–Mumps–Rubella (MMR) and pertussis vaccines, the comparison of fever rates across the different studies is not possible due to the different cut off points, routes of measurement and follow-up times reported.

Table 2 illustrates the variability of case definitions and/or case descriptions used in recent pertussis vaccine trials for the AEFI “hypotonic hyporesponsive episodes” [10,15–24]. It is debatable whether the case definitions from the various trials actually describe the same clinical entity. In addition, the definitions may also have different sensitivity and specificity, making comparability of findings across these prospective studies difficult. The inconsistency of case definitions poses the same problem for evaluation of passive surveillance data on HHE [25].

A similar variability of definitions also exists for other AEFI such as local reactions, persistent crying, and convulsion (data not shown) [5–24]. Further, we reviewed the case definitions for intussusception used in three studies of adverse events following rotavirus vaccination and also found a considerable diversity of definitions [26–28]. These three studies were retrospective and each used a different source of data (VAERS forms, MCO automated data, and chart reviews). In contrast to prospective trials, it is more difficult to use standardized case definitions for data collection in passive surveillance systems and retrospective studies. However, the use of standardized case definitions for the analysis of such data would still greatly facilitate comparability of results.

Recent efforts and new requirements from regulatory authorities to increase study sample sizes and enhance passive surveillance systems have increased the amount of safety data collected pre- and post-vaccine licensure [29,30]. However, differences in assessment methods and case definitions for AEFI still limit meaningful comparative or meta-analyses and thereby represent a major missed opportunity for advancing the science of immunization safety. The Brighton Collaboration was created to address this need and represents an important platform for international collaboration to improve immunization safety.

1. The Brighton Collaboration

The Brighton Collaboration is an independent international voluntary collaboration to facilitate the development, evaluation, and dissemination of high quality information about the safety of human vaccines. Its first task is the harmonization and standardization of case definitions of AEFI. The Collaboration is characterized by a transparent

methodology and has no financial interest in the results of the work.

The idea for the Collaboration was first presented in 1999 during an international vaccine meeting in Brighton, England [31]. The Brighton Collaboration was officially launched in autumn 2000. The Collaboration includes researchers and other professionals from vaccine safety, public health, pharmaceutical and regulatory agencies who are interested in addressing the problems of the quality of information on vaccine safety. In the European Union the work is currently carried out within the European Research Program for Improved Vaccine Safety Surveillance (EUSAFEVAC).

The Brighton Collaboration aims to develop a single case definition per AEFI of interest. Definitions are structured in a three level format to be globally applicable for all immunization safety purposes and in settings with different levels of resources. A total of 50–100 standardized case definitions of local and systemic AEFI are intended to be developed, and disseminated for global use in both pre- and post-licensure trials and in post-marketing surveillance.

Target groups for their use are investigators and health officials who carry out immunization studies, as well as healthcare workers making clinical decisions on immunizations who need to get, interpret, provide and report information on immunization safety.

2. Structure and process to develop case definitions for AEFI

A working group consisting of 5–20 participants from developed and developing countries and with diverse scientific backgrounds is formed for each AEFI to be defined. Working groups initially seek information regarding current practice by a systematic literature search and retrieval of available unpublished definitions. Based on the available evidence and consensus formation during monthly conference calls and e-mail discussions, a draft definition is developed. Subsequently, a reference group of individual experts in the field and representatives of organizations concerned with vaccine safety will be asked to review the draft definitions and to propose adjustments, if necessary, to allow for wide applicability and usefulness of the definitions. Following review by the reference group and revision by the working group, the definitions are finalized for dissemination and implementation. Cyclical revision of the definitions will be guided by further evaluation in vaccine trials and analyses of data from existing surveillance systems.

The first AEFIs to be defined are fever, local reactions, intussusception, inconsolable crying, seizure, hypotonic hyporesponsive episode, allergic reaction, rash, asthenia, paresthesia, sudden infant death syndrome, myalgia, and idiopathic thrombocytopenia. Further AEFIs will be defined in the future depending on public and/or scientific interest or urgency.

We expect The Brighton Collaboration to grow over time and expand to a global network of individuals and organizations concerned with immunization safety. Collaborators can participate either as volunteers in working groups or as organizations in the reference group. The resulting accrual of expertise focused on the development of standardized case definitions for AEFI and the sharing of knowledge within and outside the Collaboration will benefit health officials, vaccine providers, and vaccine recipients by providing high quality data to facilitate decision-making.

Every professional concerned with vaccine safety is invited to be part of this network. More information about The Brighton Collaboration can be viewed at http://brightoncollaboration.org.

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References

[1] Fescharek R, Nicolay U, Arras-Reiter C. Monitoring and safety assessment in phase I to II clinical trials. Dev Biol Stand 1998;95:203–20.
[2] The Uppsala Monitoring Centre. WHO collaborating centre for international drug monitoring: adverse reaction terminology (WHO-ART). Available at: http://www.who-umc.org/pdfs/ardguide.pdf.
[3] International Conference on Harmonization. The medical dictionary for regulatory activities. Available at: http://www.ifpma.org/ichMedDRA.html.
[4] Braun M, Terracino G, Salive, et al. Report of a US Public Health Service Workshop on HHE after pertussis immunisation. Pediatrics 1998;102:e52.
[5] King G, Markowitz L, Heath J, Redd S, Coleman S, Bellini J, et al. Antibody response to Measels-Mumps-Rubella vaccine of children with mild illness at the time of vaccination. JAMA 1996;275:704–7.
[6] Shinefield H, Black S, Staele B, et al. Safety, tolerability and immunogenicity of concomitant injections in separate locations of MMRII, Varivax and Tetramune in healthy children vs. concomitant injections of MMR II and Tetramune followed 6 weeks later by Varivax. Pediatr Infect Dis J 1998;7:980–5.
[7] Usonis V, Bakasenas V, Kaufhold A, et al. Reactogenicity and immunogenicity of a new live attenuated combined Measles, Mumps and Rubella vaccine in healthy children. Pediatr Infect Dis J 1999;18:42–8.
[8] Klinge J, Lugauer S, Korn K, et al. Comparison of immunogenicity and reactogenicity of a measles vaccinated at 9–11, 12–14 or 15–17 months of age, Mumps and Rubella (MMR) vaccine in German children. Vaccine 2000;18:3134–40.
[9] Crovari P, Gabutti G, Giamanco G, et al. The cooperative group for the study of MMR vaccines. Reactogenicity and immunogenicity of a new combined Measels-Mumps-Rubella vaccine: results of a multicenter trial. Vaccine 2000;18:2796–803.
[10] Gustafsson L, Hallander H, Olin P, et al. A controlled trial of a two component acellular, a five component acellular and a whole-cell pertussis vaccine. N Engl J Med 1996;334:349–55.

[11] Schmitt HJ, Schuind A, Knuf M, et al. Clinical experience of a tricomponent acellular pertussis vaccine combined with diphteria and tetanus toxoids for primary vaccination in 22,505 infants. J Pediatr 1996;129:695–701.
[12] Liese J, Meschievitz C, Harzer E, et al. Efficacy of a two-component acellular pertussis vaccine in infants. PIDJ 1997;16:1038–44.
[13] Schmitt-Grohé S, Stehr K, Cherry JD, Heininger U, et al. Minor adverse events in a comparative efficacy trial in Germany in infants receiving either the Lederle/Takeda acellular pertussis component DTP(DTaP) vaccine, the Lederle whole cell component DTP (DTP) or DT vaccine. Dev Biol Stand 1997;89:113–8.
[14] Simondon F, Preziosi M, Yam A, et al. A randomized double blind trial comparing a two-component acellular to a whole-cell pertussis vaccine in Senegal. Vaccine 1997;15:1606–12.
[15] Ramkissoon A, Coovadia HM, Loening WEK, et al. Does whole-cell pertussis vaccine protect black South African infants. South African Med J 1991;79:645–9.
[16] Blumberg DA, Lewis K, Mink CAM, et al. Severe reactions associated with Diphtheria-Tetanus-Pertussis vaccine: detailed study of children with seizures, hypotonic-hyporesponsive episodes, high fevers, and persistent crying. Pediatrics 1993;91:1158–65.
[17] Cody CL, Baraff LJ, Cherry JD, et al. Nature and rates of adverse reactions associated with DTP and DT immunizations in infants and children. Pediatrics 1981;68:650–60.
[18] Greco D, Salmaso S, Mastrantonio P, Guiliano M, Tozzi A, Anemona A, et al. Progretto Pertosse Working Group: a controlled trial of two acellular vaccines and one whole cell vaccine against pertussis. N Engl J Med 1996;334:341–8.
[19] Gold R, Scheifele D, Halperin S, Dery P, et al. Hypotonic-hyporesponsive episodes in children hospitalized at 10 Canadian Pediatric Tertiary-Care Centers, 1991–1994. Can Commun Dis Rep 1997; 23:73–6.
[20] Überall MA, Stehr K, Cherry JD, et al. Severe adverse events in a comparative efficacy trial in Germany in infants receiving either the Lederle/Takeda acellular pertussis componentDTP(DTaP vaccine, the Lederle whole cell component DTP (DTP) or DT vaccine. Dev Biol Stand 1997;89:83–9.
[21] Olin P, Rasmussen F, Gustafsson L, et al. Randomised controlled trial of two-component, three-component, and five-component acellular pertussis vaccines compared with whole-cell pertussis vaccine. Lancet 1997;350:1569–77.
[22] Mills E, Gold R, Thipphawong J, et al. Safety and immunogenicity of a combined five component pertussis diphtheria-tetanus-inactivated poliomyelitis-Haemophilus b conjugate vaccine administered to infants at 2, 4 and 6 months of age. Vaccine 1998;16:576–85.
[23] Goodwin H, Nash M, Gold M, Heath TC, Burgess MA. Vaccination of children following a previous hypotonic-hyporesponsive episode. J Paediatr Child Health 1999;35:549–52.
[24] Gold M, Goodwin H, Botham S, et al. Revaccination of 421 children with a past history of an adverse vaccine reaction in a special immunization service. Arch Dis Child 2000;83:128–31.
[25] Vermeer-de Bondt PE, Labadie J, Rümke HC. Rate of recurrent collapse after vaccination with whole cell pertussis vaccine: follow up study. BMJ 1998;316:902–3.
[26] Zanardi LR, Haber P, Mootrey GT, et al. Intussusception among recipients of rotavirus vaccine: reports to the vaccine adverse event reporting system. Pediatrics 2001;107:E97.
[27] Murphy TV, Gargiullo PM, Massoudi MS, et al. Intussusception among infants given an oral rotavirus vaccine. N Engl J Med 2001;344:564–72.
[28] Kramarz P, France EK, Destefano F, et al. Population-based study of rotavirus vaccination and intussusception. Pediatr Infect Dis J 2001;20:410–6.
[29] Susan S. Ellenberg. Safety Considerations for New Vaccine Development. FDA Workshop on Evaluation of New Vaccines. November, 2000. http://www.fda.gov/cber/summaries/111400se.htm.
[30] Jacobson RM, Adegbenro A, Pankratz VS, et al. Adverse events and vaccination-the lack of power and predictability of infrequent events in pre-licensure study. Vaccine 2001;19:2428–33.
[31] Chen RT. Vaccine risks: real, perceived, and unknown. Vaccine 1999; 17:S41–46.
[32] Chen RT, Rastogi SC, Mullen JR, Hayes SW, Cochi SL, Donlon JA, et al. The Vaccine Adverse Event Reporting System (VAERS). Vaccine 1994;12:542–50.